

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 31/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 00/66093</b> <b>(43) International Publication Date:</b> 9 November 2000 (09.11.00)
<b>(21) International Application Number:</b> PCT/EP00/02923 <b>(22) International Filing Date:</b> 4 April 2000 (04.04.00) <b>(30) Priority Data:</b> 9909925.1 29 April 1999 (29.04.99) GB <b>(71) Applicant (for all designated States except US):</b> PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch 1.2, I-20152 Milano (IT). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GERONI, Maria, Cristina [IT/IT]; Via Correggio, 48, I-20149 Milano (IT). RIPA-MONTI, Marina [IT/IT]; Viale Fulvio Testi, 91, I-20162 Milano (IT). CARUSO, Michele [IT/IT]; Via Desiderio, 3, I-20131 Milano (IT). SUARATO, Antonino [IT/IT]; Via degli Imbriani, 39, I-20100 Milano (IT).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> COMBINED PREPARATIONS COMPRISING ANTHRACYCLINE DERIVATIVES		
<b>(57) Abstract</b>  The present invention relates to combined preparations comprising a morpholinyl anthracycline administered in combination anticancer agents chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, which are useful anticancer therapy, particularly in the treatment of a primary or metastatic liver cancer.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**COMBINED PREPARATIONS COMPRISING ANTHRACYCLINE DERIVATIVES**

The present invention pertains to the field of neoplastic  
5 diseases therapy. In particular, the present invention  
refers to the synergic anticancer effect displayed by an  
anthracycline derivative administered in combination with at  
least another pharmaceutical substance effective in anticancer  
therapy.

10

Cancers are a leading cause of death in animals and humans;  
surgery, radiation and chemotherapy are the useful means to  
fight cancers.

In particular, combined chemotherapy, designed to treat  
15 cancer by using more than one drug in combination or  
association, is a well accepted modality of treatment of  
neoplastic diseases.

Several efforts have been and are still being undertaken in  
order to select antitumor combinations more and more active  
20 and safe to be administered to a patient suffering from a  
cancer.

The increase of the antitumor efficacy of a known antitumor  
compound by administering the same in combination with one or  
more different antitumor compounds in order to obtain a  
25 therapeutic synergy, is a strongly felt need in the field of  
anticancer therapy.

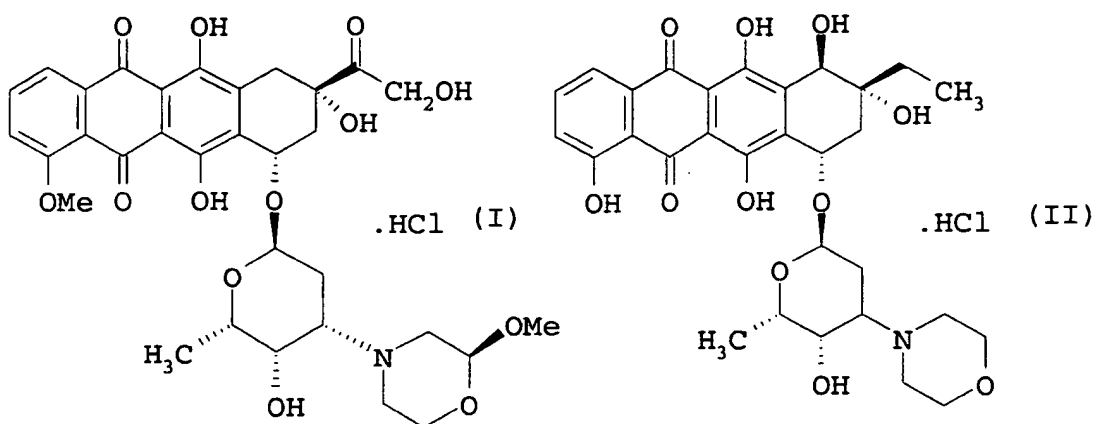
The present invention fulfill such a need by providing an  
anthracycline derivative which is morpholinyl anthracycline,  
administered in combination with at least another  
30 pharmaceutical substance effective in anticancer therapy, so  
that a synergistic effect can be revealed.

It is therefore a first object of the present invention  
combined preparations comprising a morpholinyl anthracycline  
35 administered in combination with at least another

pharmaceutical substance effective in anticancer therapy chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative.

5

Anthracycline derivatives according to this invention are morpholinyl anthracyclines having formula (I) and (II)



10

The chemical names of the morpholinyl anthracyclines of formula (I) and (II) are 3'-deamino-3'-(2-methoxy-4-morpholinyl)doxorubicin.HCl (I), also known as methoxymorpholino doxorubicin (MMDX, internal code PNU 152243), and 3'-deamino-3'-(4-morpholinyl)-13-deoxy-10-hydroxycarminomycin (II), also known as MX2.

MMDX is a doxorubicin derivative obtained with the substitution of the  $-NH_2$  at position 3' in the sugar moiety with a methoxymorpholino group. This compound, synthesised in the course of a research program aimed at identifying new anthracyclines with at least partially novel modes of action and possessing broad spectrum of activity, was disclosed and claimed in Bargiotti et al., US patent NO. 4,672,057.

MMDX is active *in vitro* and *in vivo* on tumor cells resistant to anthracyclines and presenting the mdr phenotype, this last mechanism being recognised to occur also in man.

No cross-resistance was observed on tumor cells resistant to L-PAM or cisplatin (cDDP), or on cells resistant to Topoisomerase II inhibitors (at-multidrug resistant).

MMDX is active after i.p., i.v. or oral administration, with  
5 good antitumor activity on murine leukemias, and on solid murine and human tumor models.

The compound differs from most anthracyclines in being highly potent when administered *in vivo*, the optimal i.v. dose being at least 80 fold less than that of doxorubicin.

10 The high lipophilicity of the molecule, which confers to the compound the ability to reach high intracellular concentrations and is most likely one of the reasons of its efficacy on resistant models, makes it effective also after oral administration.

15

MX2, a morpholinyl anthracycline belonging to the family of 3'-deamine-3'-(4-morpholinyl) derivatives of 10-hydroxy-13-deoxocarminomycin, was described and claimed in Otake et al., US patent no. 4,710,564.

20 MX2 is active *in vitro* and *in vivo* on tumor cells resistant to anthracyclines and presenting mdr phenotype.

No cross-resistance was observed on tumor cells resistant to CTX, L-Pam and cDDP.

MX2 is active *in vivo* after i.p., i.v. and oral  
25 administration, with good antileukemic and antitumor activity on murine and human tumor models. MX2 is highly lipophilic and less cardiotoxic than Doxorubicin. The major dose limiting factor of MX2 is myelosuppression.

30 Among pharmaceutical substances effective in anticancer therapy which may be used in association or in combination with a morpholinyl anthracycline of formula (I) or (II) as defined above, there may be mentioned alkylating agents such as, e.g., mitomycin C, cyclophosphamide, busulfan, ifosfamide,  
35 isosfamide, melphalan, hexamethylmelamine, thiotepa, chlorambucil, or dacarbazine; antimetabolites such as, e.g.,

gemcitabine, capecitabine, 5-fluorouracil, cytarabine, 2-fluorodeoxy cytidine, methotrexate, idatrexate, tomudex or trimetrexate; topoisomerase II inhibitors such as, e.g., doxorubicin, epirubicin, etoposide, teniposide or  
5 mitoxantrone; topoisomerase I inhibitors such as, e.g., irinotecan (CPT-11), 7-ethyl-10-hydroxy-camptothecin (SN-38) or topotecan; antimitotic drugs such as, e.g., paclitaxel, docetaxel, vinblastine, vincristine or vinorelbine; and platinum derivatives such as, e.g., cisplatin, oxaliplatin,  
10 spiroplatinum or carboplatinum.

As used herein, "anticancer therapy" refers to all types of therapies for treating cancers or neoplasms or malignant tumors found in mammals comprising humans, including  
15 leukemias, melanoma, liver, breast, ovary, prostate, stomach, pancreas, lung, kidney, colon and central nervous system tumors.

The administration of the constituents of the combined  
20 preparations of the present invention can be made simultaneously, separately or sequentially.

It is therefore another object of the present invention the simultaneous, separate or sequential use of the combined preparations of the invention in anticancer therapy.

25 As an example, a morpholinyl anthracycline of formula (I) or (II) as defined above can be administered before the other anticancer drug; a particular example refers to the morpholinyl anthracycline of formula (I) administered on day 1 and 2 followed by cisplatin on day 3.

30

A preferred combined preparation according to the invention comprises a morpholinyl anthracycline of formula (I) or (II) as defined above and a platinum derivative, in particular cisplatin. A more preferred combined preparation according to  
35 the invention comprises a morpholinyl anthracycline of formula

(I) and cisplatin.

As already said, combined preparations according to the invention may be used in anticancer therapy. In a preferred embodiment, combined preparations of the invention may be useful for treating a liver cancer, for example a liver cancer primarily confined to the liver such as, e.g. an hepatocellular carcinoma or a cholangiocarcinoma, or liver metastases.

10

The constituents of the combined preparations according to the invention can be administered to a patient in any acceptable manner that is medically acceptable including orally, parenterally, or with locoregional therapeutic approaches such as, e.g., implants. Oral administration includes administering the constituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, lozenges, suspensions, solutions, emulsions, powders, syrups and the like. Parenteral administration includes administering the constituents of the combined preparation by subcutaneous, intravenous or intramuscular injections. Implants include intra arterial implants, for example an intrahepatic artery implant.

15

Injectations and implants are preferred administration routes because they permit precise control of the timing and dosage levels used for administration.

20

25

For example, for treating a patient suffering from a liver cancer as defined above, simultaneous, separate or sequential intrahepatic administration of the constituents of the combined preparation may be performed via the hepatic artery. More precisely, the constituents of the combined preparation may be administered to a patient with either a hepatic metastatic cancer, or with previously untreated primary liver carcinoma, via the hepatic artery directly into the lateral entry of an i.v. line inserted into the bung of an intrahepatic potacath or via a catheter inserted into the hepatic artery.

30

35

In a particular embodiment of the present invention, MMDX may be administered via the hepatic artery as an infusion; the appropriate dose of MMDX, preferably previously dissolved in saline solution, may be mixed with a suitable amount, for example an amount ranging from 1 ml to 100 ml of an agent, for example iodized oil (LIPIODOL™), which remains selectively in a liver tumor after its injection through the hepatic artery. The actual preferred method and order of administration of the constituents of the combined preparation of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the morpholinyl anthracycline (I) or (II) as defined above being utilized, the particular pharmaceutical formulation of the other anticancer agent being utilized, the particular cancer being treated, the severity of the disease state being treated, and the particular patient being treated. The dosage ranges for the administration of the combined preparations according to the invention may vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments, in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

The present invention also provides, in another aspect, products containing a morpholinyl anthracycline of formula (I) or (II) as defined above and at least another anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.



The present invention also relates to pharmaceutical compositions comprising, mixed together, two or more active constituents of the combined preparations according to the invention and a pharmaceutically acceptable carrier or  
5 excipient.

It is therefore a further object of the present invention a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as an active ingredient, a morpholinyl anthacycline of formula (I) or (II) as defined  
10 above and at least another anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative.

Pharmaceutical compositions according to the invention are  
15 useful in anticancer therapy. In particular, they may be useful for treating a liver cancer as defined above.

Pharmaceutically acceptable carriers or excipients to be utilized in the preparation of a pharmaceutical composition according to the invention are well known to people skill in  
20 the art of formulating compounds in a form of pharmaceutical compositions.

For example, such pharmaceutical compositions may routinely contain, e.g., pharmaceutically acceptable salts, buffering agents, preservatives and/or compatible carriers. As used  
25 herein, "pharmaceutically acceptable carrier" refers to one or more compatible solid or liquid filler, diluent or encapsulating substances which are suitable for administration to mammals including humans.

Pharmaceutical compositions suitable for parenteral or  
30 intrahepatic administration are formulated in a sterile form. The sterile composition thus may be a sterile solution or suspension in a non-toxic parenterally acceptable diluent or solvent.

Pharmaceutical compositions for intrahepatic administration  
35 are formulated, for example, in a form which remains

selectively in a liver tumor after their injection through the hepatic artery; LIPIODOL™ is a suitable carrier of anticancer agents which can be used for intrahepatic administration.

5 The amount of an active ingredient contained in the pharmaceutical composition according to the invention may vary quite widely depending upon many factors such as e.g. the administration route and the vehicle.

As an example, the pharmaceutical composition of the invention may contain from 0.1 mg to 100 mg of MMDX and from 1 mg to  
10 1000 mg of a platinum derivative such as cisplatin.

A further aspect of the present invention is to provide a method of treating a mammal including a human, suffering from a cancer comprising administering to said mammal a morpholinyl  
15 anthracycline of formula (I) or (II) as defined above and at least another anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in amounts effective to produce a synergistic  
20 anticancer effect.

A still further aspect of the present invention is to provide a method for lowering the side effects caused by anticancer therapy with an anticancer agent in mammals, including  
25 humans, in need thereof, the method comprising administering to said mammal a combined preparation comprising a morpholinyl anthracycline of formula (I) or (II) as defined above and at least another anticancer agent chosen from an alkylating agent, an antimetabolite a topoisomerase II inhibitor, a  
30 topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in amounts effective to produce a synergistic anticancer effect.

In particular, the present invention provides a method of treating patients suffering from a primary or metastatic liver  
35 cancer.

By the term "a synergistic anticancer effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of a morpholinyl anthracycline of formula (I) or (II) as defined above and at least another anticancer agent chosen from an alkylating agent, an antimetabolite a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in amounts effective to produce a synergistic anticancer effect to mammals, including humans.

By the term "administered" or "administering" as used herein is meant parenteral and /or oral and/or locoregional administration, as defined above. In the method of the subject invention, the morpholinyl anthracycline may be administered simultaneously with at least another anticancer agent chosen from an alkylating agent, an antimetabolite a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the morpholinyl anthracycline of formula (I) or (II) being utilized, the particular formulation of the alkylating agent, of the antimetabolite, of the topoisomerase II inhibitor, of the topoisomerase I inhibitor, of the antimitotic drug or of the platinum derivative being utilized, the particular tumor model being treated, and the particular host being treated.

In the method of the subject invention, for the administration of the morpholinyl anthracycline of formula (I) or (II), the course of therapy generally employed is from about 0.1 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup> of body surface area. More preferably, the course of therapy employed is from about about 1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the alkylating agent the course of therapy generally employed is from about 10 mg/m<sup>2</sup> to about 100,000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is  
5 from 180 mg/m<sup>2</sup> to about 16,000 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the antimetabolite the course of therapy generally employed is from about 0.1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is  
10 from 0.2 mg/m<sup>2</sup> to about 500 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the topoisomerase II inhibitor the course of therapy generally employed is from about 1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy  
15 employed is from 10 mg/m<sup>2</sup> to about 500 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the topoisomerase I inhibitor the course of therapy generally employed is from about 1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of  
20 body surface area. More preferably, the course therapy employed is from 100 mg/m<sup>2</sup> to about 500 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the antimitotic drug the course of therapy generally  
25 employed is from about 1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is from 10 mg/m<sup>2</sup> to about 500 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the platinum derivative the course of therapy generally  
30 employed is from about 1 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is from 10 mg/m<sup>2</sup> to about 500 mg/m<sup>2</sup> of body surface area.

As already said, the anticancer therapy of the present invention is suitable for treating, e.g. breast, ovary,  
35 prostate, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukaemiae and central nervous system tumors in

mammals, including humans; in particular it is suitable for treating a liver cancer.

The present invention also provides a therapeutic kit comprising, in suitable container means, a pharmaceutical formulation of a morpholinyl anthacycline of formula (I) or (II) as defined above and a pharmaceutical formulation of at least another anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative. For example, in a kit according to the invention, the morpholinyl anthacycline and at least another anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative are present within a single container means or within distinct container means. As a particular example, a kit comprises a pharmaceutical formulation of the morpholinyl anthracycline of formula (I) as defined above and a pharmaceutical formulation of cisplatin, within distinct container means.

Kits according to the invention are intended for use in anticancer therapy as defined above, in particular for the treatment of a liver cancer.

As stated above, the effect of the combined administration of a morpholinyl anthracycline of formula (I) or (II) as defined above and of at least another pharmaceutical substance effective in anticancer therapy such as an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug or a platinum derivative, is significantly increased (synergic effect) without a parallel increased toxicity.

In other words, the combined therapy of the present invention enhances the anticancer effects of the morpholinyl anthracycline (I) or (I) as defined above and of the other anticancer substance and thus yields the most effective and

least toxic treatment for cancers.

The superadditive actions of the combined preparations of the present invention are shown, for instance, by the following *in vivo* tests, which are illustrative, but not limiting of the combined preparations and methods of the present invention. Other suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are within the scope of this invention.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia, (originally obtained from NCI) obtained combining the morpholinyl anthracycline of formula (I) (PNU-152243) with cisplatin (cDDP), a platinum derivative, which is a representative pharmaceutical substance effective in anticancer therapy.

Table 1: Antileukemic activity against disseminated L1210<sup>1</sup> murine leukemia of PNU-152243 in combination with cDDP

Compound	Treatment schedule	Dose <sup>2</sup> (mg/Kg/day)	ILS% <sup>3</sup>	Tox <sup>4</sup>	Statistical Analysis Two Ways ANOVA
PNU-152243	iv +1,2	0.05	50	0/10	
cDDP	iv +3	5.9 7.7	33 33	0/10 0/10	
PNU-152243 + cDDP	iv+1,2  iv+3	0.05  5.9	  83	  0/10	P=0.0034 Synergistic effect
PNU-152243 + CDDP	iv+1,2  iv+3	0.05  7.7	  100	  0/10	P=0.0036 Synergistic effect

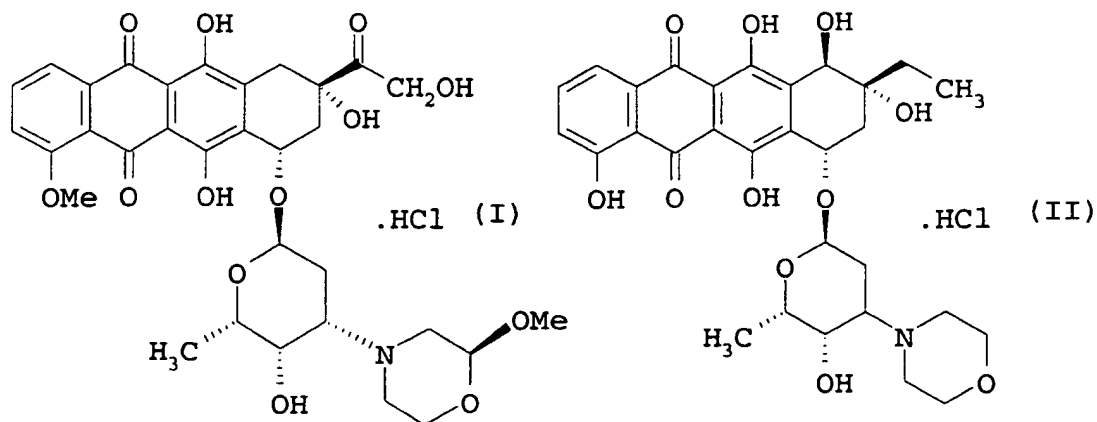
1) L1210 murine leukemia was maintained in DBA/2 mice by weekly ip passages of 10<sup>5</sup> cells/mouse - For experiments, 10<sup>5</sup> cells/mouse were injected iv in CD2F1 mice on day 0.

2) Treatment is given starting on day 1 after tumor transplantation (day 0)

- 3) Increased in Life Span [(Median survival time of treated mice/median survival time of controls) x 100]-100
- 4) Number of toxic deaths/number of mice
- 5 The above reported data show that at doses of 5.9 and 7.7 mg/kg of cDDP administered alone on day 3, and at the dose of 0.05 mg/kg of PNU 152243 administered alone on day 1 and 2, were associated, without toxicity, ILS% values of 33, 33 and 50, respectively.
- 10 Data obtained combining administration of 0.05 mg/kg PNU 152243 on day 1 and 2 and 5.9 or 7.7 mg/kg of CDDP on day 3, clearly indicates a significant increase (synergistic effect) in ILS% (83 and 100 respectively), demonstrating an actual therapeutic advantage of the combination in comparison with
- 15 each drug administered alone.

CLAIMS

1. A combined preparation which comprises a morpholinyl anthracycline of formula (I) or (II)



and an anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative.

2. A preparation according to claim 1, wherein the alkylating agent is chosen from mitomycin C, cyclophosphamide, busulfan, ifosfamide, isosfamide, melphalan, hexamethylmelamine, thiotepa, chlorambucil, and dacarbazine.

3. A preparation according to claim 1, wherein the antimetabolite is chosen from gemcitabine, capecitabine, 5-fluorouracil, cytarabine, 2-fluorodeoxy cytidine, methotrexate, idatrexate, tomudex and trimetrexate.

4. A preparation according to claim 1, wherein the topoisomerase II inhibitor is chosen from doxorubicin, epirubicin, etoposide, teniposide and mitoxantrone.

5. A preparation according to claim 1, wherein the topoisomerase I inhibitor is chosen from irinotecan (CPT-11), 7-ethyl-10-hydroxy-camptothecin (SN-38) and topotecan.



6. A preparation according to claim 1, wherein the antimitotic drug is chosen from paclitaxel, docetaxel, vinblastine, vincristine and vinoreblin.

5

7. A preparation according to claim 1, wherein the platinum derivative is chosen from cisplatin, oxaliplatin, spiroplatinum and carboplatinum.

10 8. A preparation according to claim 7, wherein the platinum derivative is cisplatin.

9. A preparation according to claim 1 which comprises a morpholinyl anthracycline of formula (I) and cisplatin.

15

10. A preparation according to any one of claims 1 to 9 which is formulated as a pharmaceutical composition comprising, in addition, a pharmaceutically acceptable carrier or excipient.

20 11. A preparation as defined in one of claims 1 to 10 for use in anticancer therapy.

12. A preparation according to claim 11, wherein the anticancer therapy is liver cancer therapy.

25

13. A preparation according to claim 13, wherein the liver cancer is a cancer primarily confined to the liver or is a liver metastase.

30 14. A preparation according to claim 13 wherein the cancer primarily confined to the liver is an hepatocellular carcinoma or a cholangiocarcinoma.

15. Products containing a morpholinyl anthracycline of formula (I) or (II) as defined in claim 1 and an anticancer

35

agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

16. Products according to claim 15, wherein the anticancer therapy is liver cancer therapy.

10 17. Products according to claim 16, wherein the liver cancer is a cancer primarily confined to the liver or is a liver metastase.

15 18. Products according to claim 17, wherein the cancer primarily confined to the liver is an hepatocellular carcinoma or a cholangiocarcinoma.

19. Products according to any one of claims 15 to 18, wherein the morpholinyl anthracycline and the said anticancer agent are for separate or sequential use.

20 20. Products according to claim 19 wherein the morpholinyl anthracycline is for administration before the said anticancer agent.

25

21. Products according to any one of claims 15 to 21, wherein the morpholinyl anthracycline is for administration on days 1 and 2 and the anticancer agent is for administration on day 3.

30 22. Products according to any one of claims 15 to 21, wherein the morpholinyl anthracycline is of formula (I) and the said anticancer agent is cisplatin.

23. Products according to any one of claims 15 to 22, formulated for intrahepatic administration.

35

24. Products according to any one of claims 15 to 23, wherein the alkylating agent is chosen from mitomycin C, cyclophosphamide, busulfan, ifosfamide, isosfamide, melphalan, 5 hexamethylmelamine, thiotepa, chlorambucil, and dacarbazine.

25. Products according to one of claims 15 to 24, wherein the antimetabolite is chosen from gemcitabine, capecitabine, 5-fluorouracil, cytarabine, 2-fluorodeoxy cytidine, 10 methotrexate, idatrexate, tomudex and trimetrexate.

26. Products according to one of claims 15 to 24, wherein the topoisomerase II inhibitor is chosen from doxorubicin, epirubicin, etoposide, teniposide and mitoxantrone.

15

27. Products according to one of claims 15 to 24, wherein the topoisomerase I inhibitor is chosen from irinotecan (CPT-11), 7-ethyl-10-hydroxy-camptothecin (SN-38) and topotecan.

20 28. Products according to one of claims 15 to 24 wherein the antimitotic drug is chosen from paclitaxel, docetaxel, vinblastine, vincristine and vinorelbine.

25 29. Products according to one of claims 15 to 24, wherein the platinum derivative is chosen from cisplatin, oxaliplatin, spiropalladium and carboplatinum.

30 30. Products according to claim 29, wherein the platinum derivative is cisplatin.

30

31. Products containing a morpholinyl anthracycline of formula (I) as defined in claim 1 and cisplatin, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

32. Products as defined in one of claims 15 to 31, formulated for intrahepatic administration.

33. Use of a morpholinyl anthracycline of formula (I) or (II)  
5 as defined in claim 1 and an anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in the preparation of a medicament for use in anticancer therapy, wherein the morpholinyl  
10 anthracycline and the said anticancer agent are administered simultaneously, separately or sequentially.

34. Use according to claim 33, wherein the alkylating agent is chosen from mitomycin C, cyclophosphamide, busulfan,  
15 ifosfamide, isosfamide, melphalan, hexamethylmelamine, thiotepa, chlorambucil, and dacarbazine.

35. Use according to claim 33, wherein the antimetabolite is chosen from gemcitabine, capecitabine, 5-fluorouracil,  
20 cytarabine, 2-fluorodeoxy cytidine, methotrexate, idatrexate, tomudex and trimetrexate.

36. Use according to claim 33, wherein the topoisomerase II inhibitor is chosen from doxorubicin, epirubicin, etoposide,  
25 teniposide and mitoxantrone.

37. Use according to claim 33, wherein the topoisomerase I inhibitor is chosen from irinotecan (CPT-11), 7-ethyl-10-hydroxy-camptothecin (SN-38) and topotecan.  
30

38. Use according to claim 33, wherein the antimitotic drug is chosen from paclitaxel, docetaxel, vinblastine, vincristine and vinoreblin.

35 39. Use according to claim 33, wherein the platinum derivative

is chosen from cisplatin, oxaliplatin, spiropatinum and carboplatinum.

40. Use according to any one of claims 33 to 39 wherein the  
5 morpholinyl anthacycline is of formula (I) and the anticancer agent is cisplatin.

41. Use according to any one of claims 33 to 40, wherein the  
10 anticancer therapy is liver cancer therapy.

42. Use according to claim 41 wherein the liver cancer is a  
cancer primarily confined to the liver or is a liver  
metastase.

15 43. Use according to claim 42 wherein the cancer primarily confined to the liver is an hepatocellular carcinoma or a cholangiocarcinoma.

20 44. Use according to any one of claims 33 to 43, wherein the medicament is formulated for intrahepatic administration.

45. Use according to any one of claims 33 to 44 wherein the  
morpholinyl anthracycline is administered before the said  
anticancer agent.

25 46. Use according to any one of claims 33 to 45 wherein the morpholinyl anthracycline is administered on days 1 and 2 and the said anticancer agent is administered on day 3.

30 47. A therapeutic kit comprising, in suitable container means, a pharmaceutical formulation of a morpholinyl anthacycline of formula (I) or (II) as defined in claim 1 and a pharmaceutical formulation of an anticancer agent chosen from an alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a  
35 topoisomerase I inhibitor, an antimitotic drug and a platinum

derivative.

48. A kit according to claim 47, wherein the morpholinyl anthracycline and the anticancer agent are present within a  
5 single container means.

49. A kit according to claim 47, wherein the morpholinyl anthracycline and the anticancer agent are present within distinct container means.

10

50. A kit according to any one of claims 47 to 49, wherein the morpholinyl anthracycline is of formula (I) and the said anticancer agent is cisplatin.

15 51. A kit according to any one of claims 47 to 50 for use in anticancer therapy.

52. A kit according to claim 51 wherein the anticancer therapy is liver cancer therapy.

20

53. A kit according to claim 52 wherein the liver cancer is a cancer primarily confined to the liver or is a liver metastase.

25 54. A kit according to claim 53 wherein the cancer primarily confined to the liver is an hepatocellular carcinoma or a cholangiocarcinoma.

30 55. A kit according to any one of claims 47 to 54, in which the components are formulated for intrahepatic administration.

56. A method of treating a mammal including a human, suffering from a cancer, which method comprises administering to said mammal a morpholinyl anthracycline of formula (I) or (II) as  
35 defined in claim 1 and an anticancer agent chosen from an

alkylating agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in amounts effective to produce a synergistic anticancer effect.

5

57. A method according to claim 56, wherein the cancer is a liver cancer.

58. A method for lowering the side effects caused by  
10 anticancer therapy with an anticancer agent in mammals, including humans, which method comprises administering to a mammal in need thereof a combined preparation comprising a morpholinyl anthacycline of formula (I) or (II) as defined in claim 1 and an anticancer agent chosen from an alkylating  
15 agent, an antimetabolite, a topoisomerase II inhibitor, a topoisomerase I inhibitor, an antimitotic drug and a platinum derivative, in amounts effective to produce a synergistic anticancer effect.

20 59. A method according to claim 58, wherein the cancer is a liver cancer.